

Long term outcomes of pharmacological treatments for opioid dependence: does methadone still lead the pack?

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The aim of this review was to update and summarize the scientific knowledge on the long term outcomes of the different pharmacological treatment options for opioid dependence currently available and to provide a critical discussion on the different treatment options based on these results. We performed a literature search using the PubMed databases and the reference lists of the identified articles. Data from research show that the three pharmacological options reviewed are effective treatments for opioid dependence with positive long term outcomes. However, each one has its specific target population and setting. While methadone and buprenorphine are first line options, heroin-assisted treatment is a second line option for those patients refractory to treatment with methadone with concomitant severe physical, mental, social and/or functional problems. Buprenorphine seems to be the best option for use in primary care offices. The field of opioid dependence treatment is poised to undergo a process of reinforcement and transformation. Further efforts from researchers, clinicians and authorities should be made to turn new pharmacological options into clinical reality and to overcome the structural and functional obstacles that maintenance programmes face in combatting opioid dependence.

Introduction

Opioid dependence is considered a chronic, relapsing disorder that leads to increased morbidity and mortality. In addition, it is associated with impaired patient functioning and quality of life, and with social and economic consequences. Despite this, the Office of Applied Studies [1] found that the majority of subjects with drug addiction receive no treatment at all.

Having a chronic, relapsing disorder, opioid-dependent patients will benefit from treatments including continuing care and close monitoring over time as well as patients with other physical and mental disorders [2]. Long term substitution therapy (methadone, buprenorphine and buprenorphine/naloxone) constitutes an effective and well-established treatment option. However outcomes are maximized when it forms part of a compre-

hensive and individualized treatment plan including counselling and psychosocial interventions. Evaluation of methadone maintenance treatments in the European Union has demonstrated positive outcomes in terms of illegal substance use, health status and risk behaviours, criminal activity, functioning and quality of life [3, 4] although a subgroup of patients resistant to such treatment has been reported (discontinuation and/or illicit heroin use while on methadone) [5]. Consequently, different maintenance therapy alternatives have been developed.

The aims of this review were to update and summarize the scientific knowledge on the long term outcomes of the different pharmacological treatment options for opioid dependence currently available and to provide a critical discussion on the different treatment options based on these results.

Methods

This is a selective review of data on the state of long term outcomes of pharmacological treatments for opioid dependence [6].

Information sources

A search was performed in the PubMed databases using the following search statements 'Outcomes [Title] OR Follow-up [Title]' AND 'Heroin addicts [All Fields] OR Opioid dependence [All Fields]' AND 'Methadone [All Fields] OR Diacetylmorphine [All Fields] OR Heroin-assisted treatment [All Fields] OR LAAM [All Fields] OR Buprenorphine [All Fields]'. As the opioid dependence phenomenon and its treatment have changed over time, we searched only for articles published in the last 10 years to ensure their relevance and comparability.

A total of 140 articles were obtained. Articles were considered relevant if they (i) described long term outcomes (>9 months) or (ii) reflected upon the pros and cons of the different therapeutic options. In addition to the database search, we searched the reference lists of the identified articles for additional relevant references.

Results

Long term outcomes of methadone maintenance treatment

Methadone was introduced in the 1960s and is currently the most commonly approved and used pharmacological maintenance option for the treatment of opioid dependence [7].

The main results of its long term use are summarized in Table 1. All the identified studies were uncontrolled studies with large patient samples, with follow-up periods ranging from 6 months [6] to 30 years [8]. They evaluated different outcomes, which we grouped under the following headings: retention rate and drug use, health status and risk behaviours, criminal activity, functioning and quality of life.

Almost all studies found high retention rates ranging from 84% at 1 year [9] to about 70% at 1 year [10, 11], 18 months [12], 2 years [9] and 6 years [13] of follow-up. However, the study of Gossop *et al.* [14] showed the opposite, i.e. a 2 year retention rate of 30% in methadone maintenance treatment (MMT), whether administered at drug clinics or by general practitioners.

With respect to drug use, all studies agreed that there was a significant reduction in use of the drugs studied (heroin, non-prescribed methadone, benzodiazepines, cocaine and/or alcohol) identified both by self-reports and/or urine drug screens. In addition, Davstad *et al.* [9] found a higher relative risk for illicit drug use in discharged patients compared with those who remained in treatment, and Fernández-Miranda *et al.* [13, 15, 16] reported a significant decrease in overdoses between baseline and 6 year follow-up.

Results for health status and risk behaviours were in the same direction. All studies found significant reductions in risk behaviours (intravenous drug use, shared use of injection paraphernalia and sexual risk behaviours) [6, 14, 16–18] and in health problems (physical and mental) [12, 14, 18, 19]. It is worth noting that, with respect to the latter, there were two exceptions; Coviello *et al.* [17] who found a significantly higher number of patients receiving psychiatric treatment among those who were in MMT and Fernández-Miranda *et al.* [16] who reported a non-significant increase in the rate of patients diagnosed with HCV (from 78% to 90%) and HIV (from 28.6% to 35.7%) during the 6 years of follow-up.

Studies also demonstrated significant reductions in criminal activities as determined by rates of incarceration [17], probability of arrests [20], illegal incomes [6], frequency of crime [18, 19], and Addiction Severity Index (ASI) legal composite score [19]. Finally, for functioning and quality of life, although less studied, the results were consistent: significant increase in productivity [6, 19], significant improvement in ASI family/social composite score [19], and significant improvement in well-being as determined by the Christchurch Inventory score [21].

Long term outcomes of other agonist maintenance treatments

Buprenorphine, buprenorphine/naloxone Along with maintenance on methadone, maintenance on buprenorphine is the commonest pharmacological maintenance treatment option for opioid-dependent patients. Buprenorphine monotherapy is approved for opioid addiction treatment in almost all European countries and in Australia, Canada, Indonesia, Israel, Malaysia, Singapore, South Africa, Taiwan and the United States. Buprenorphine/naloxone is approved in the same countries, with the exception of Malta and Switzerland, and is pending approval in Israel.

Research on long term outcomes of buprenorphine maintenance treatment (BMT) is limited by small numbers of patients and short duration of follow-up. In fact, only four studies (see Table 2) included relatively large samples that were followed for more than 12 months.

Studies showed high 1 year retention rates ranging from 90% [22, 23] to almost 60% [23]. In addition they demonstrated a greater significant reduction in the percentage of opioids and cocaine in negative urine tests compared with methadone treatment [22], and a significant reduction in self-reported drug use in those patients retained in treatment [24]. Health status in terms of HIV treatment and achievement of viral suppression [25], and social and educational functioning significantly improved [22].

Heroin-assisted treatment (HAT) The use of heroin as a therapeutic approach to long term treatment of opioid addiction has been proposed for overcoming cravings and

Table 1

Long term outcomes of methadone maintenance treatment for opioid dependence

First author, year (reference)	Design, n	Intervention	Results
Retention in treatment, drug use and overdose			
Grella, 2012 [8]	30 year follow-up 343 subjects who were enrolled in MMT at some point in 1976–78		Past year drug use: any illicit drug = 37.9%; heroin/other opioids = 20.1%; cocaine/crack = 8.8%; marijuana = 22.2%; amphetamines = 10.5%; tranquilizers = 4.4% (no gender differences) Past-year alcohol use = 35.1% (no gender differences) Past-year drug Tx = 37.6% (no gender differences)
Coviello, 2011 [17]	9 month follow-up 230 discharged from a MTTP in need of Tx: – 102 re-engaged – 128 not re-engaged	102 in MMT (Tx) 128 not re-engaged (No Tx): – 6 week outreach case management for re-engaging in Tx – passive referral for Tx	Retention in Tx (%): significantly higher in the Tx group (65 vs. 23, $P < 0.001$) Heroin use in the last 30 days (self-reported): significantly lower in the Tx group (Tx = 2.7 vs. No Tx = 11.3, $P < 0.001$) Urine drug screens (% positive): significantly lower for opioids in the Tx group (Opioids: 29 vs. 58, $P < 0.001$)
Jimenez-Treviño, 2011 [47]	25 year follow-up 214 heroin addicts who were enrolled in MMT in 1980–84		Survivors sample (53 subjects): current MMT = 39.6% (males 50%, females 37.5%); current heroin use = 22.6% (males 32.5% vs. females 0%, $P < 0.05$)
Comiskey, 2010 [10]	1 year follow-up 215	3 MMTP settings: – 48 community-based clinics (CS) – 113 health board clinics (HB) – 54 general practitioners surgeries (GP)	Retention in index Tx: CS = 71%; HB = 70%; GP = 67% Heroin abstinence: significant increase for the three Tx settings (CS = from 11% at baseline to 45% at follow-up, $P < 0.01$; HB = from 6% to 33%, $P < 0.01$; GP = from 43% to 78%, $P < 0.01$) Non-prescribed methadone abstinence: significant increase for the three Tx settings (CS = from 56% to 82%, $P < 0.05$; HB = from 41% to 83%, $P < 0.01$; GP = from 70% to 90%, $P < 0.05$) Benzodiazepine abstinence: significant increase for two Tx settings (CS = from 53% to 73%, $P < 0.05$; GP = from 78% to 98%, $P < 0.05$) Cocaine abstinence: significant increase for two Tx settings (CS = from 56% to 78%, $P < 0.05$; HB = from 55% to 77%, $P < 0.05$)
Litchfield, 2010 [21]	1 year follow-up 34 female sex-workers	MMT (usually) plus the following as required: (i) sexual health interventions and advice, (ii) specialized key working intervention, (iii) psychosocial interventions	Heroin use (% positive urine): reduction (from 87% at baseline to 72% at follow-up)
Astals, 2009 [12]	18 month follow-up 189	Low-threshold MMTP	Retention in Tx = 68.5%
Corsi, 2009 [6]	6 month follow-up 160	MMT plus one of the following: (i) risk reduction, (ii) motivational interviewing, (iii) strengths-based case management	Times injected heroin: significant reduction (from 98.3 at baseline to 51.2 at follow-up, $P < 0.001$)
Davstad, 2007 [9]	6 month to 6 year follow-up 204	MMT plus (i) structured individual counseling and/or (ii) more structured group treatment programme	Retention rate: 1 year = 84%; 2 year = 65% – Low methadone dose and younger age predicted discharge from Tx Positive urine samples: significantly lower in those who remained in Tx (9% vs. 21%) Relative risk for illicit drug use in discharged patients 2.3 (compared with those who remained in Tx)
Peles, 2006 [11]	1 year follow-up 492	MMT	1 year retention rate = 74.4% Drug use: heroin (stopped using) = 65.8%; Drug abuse: net decrease (% patients who stopped – % patients who started): cocaine = 61.6%; benzodiazepines = 10.2%; THC = 43.2%; amphetamines = 75.3%
Gossop, 2003 [14]	1 year follow-up 732	National Treatment Outcome Research Study (NTORS) 8 inpatient drug dependence units 15 residential rehabilitation units 16 methadone maintenance clinics 15 methadone reduction programmes	Abstinent from all illicit target drugs at follow-up = 22% Drug use: the greatest reductions for all drug use at follow-up were achieved in the non-injected group and the lowest by the shared injection paraphernalia group ($P < 0.001$) Alcohol use – frequency: the greatest reduction was found in the abstinent group (from 24.8 at baseline to 11.2 at follow-up) while the shared injection paraphernalia group reported an increase (from 21.1 to 28.4) ($P < 0.001$)

Table 1

Continued

First author, year (reference)	Design, <i>n</i>	Intervention	Results
Gossop, 2003 [18]	2 year follow-up 240	MMT settings: general practitioners (GP) or drug clinics (DC)	2 year retention rate: GP = 32%; DC = 30% Drug use: significant reductions from intake to follow-up for heroin, non-prescribed methadone, non-prescribed benzodiazepines and stimulants ($P < 0.001$) in both setting groups
Cacciola, 2001 [19]	7 month follow-up 310 opioid-dependent patients (278 at follow-up) – 69 substance use only (SU) – 25 SU + axis I disorder (SU1) – 95 SU + axis II disorder (SU2) – 89 SU + axis I and II disorders (SU1 + 2)	MMT plus individual counseling	Retention rate at follow-up: SU = 82.4%, SU+1 = 82.6%, SU+2 = 67.2%, SU1 + 2 = 65.1% Drug use (% of positive urine test): heroin: SU = 52.7%, SU+1 = 40.9%, SU+2 = 42.7%, SU1 + 2 = 50%; cocaine: SU = 45.5%, SU+1 = 50.0%, SU+2 = 49.3%, SU1 + 2 = 45.6%; benzodiazepines: SU = 18.9%, SU+1 = 27.3%, SU+2 = 36.5%, SU1 + 2 = 30.3% ASI drug composite: significant decrease at follow-up ($P < 0.001$) Days of heroin use: significant decrease at follow-up ($P < 0.001$) Days of marijuana use: significant decrease at follow-up ($P = 0.002$) Days cocaine use: significant decrease at follow-up ($P < 0.001$) ASI alcohol composite: significant decrease at follow-up ($P = 0.016$)
Fernández-Miranda, 2001 [13], 2001 [15], 2001 [16]	6 year follow-up 132 opioid-dependents who were enrolled in MMT in 1991–92	Medium-threshold MMT	6 year retention rate = 70.9% (31.8% when only those who remained in treatment were analysed; 46.2% when discharged clinic patients are included) Drug use (% of patients who reported abstinence in the month prior to follow-up): significant decrease in heroin use (from 100% at baseline to 11.9% at follow-up, $P < 0.001$) and in cocaine use (from 31% to 14.3%, $P < 0.05$) Overdose: significant decrease (from 33.3% at baseline to 0% at follow-up, $P < 0.001$)
Health status and risk behaviours Grella, 2012 [8]	30 year follow-up 343 subjects who were enrolled in MMT at some point in 1976–78		Past year injected drugs = 18.7% (no gender differences) Poor health status (self-reported) = 16.7% (males 8.4% vs. females 27.3%, $P < 0.001$) Chronic physical health problems (only those with prevalence >20% shown): dental problems = 64.1%; back/neck problems = 51.9%; arthritis = 50.7% (males 45% vs. females 57.9%, $P < 0.05$); hypertension = 42.9%; heart disease = 26.8 (males 19.4% vs. females 36.23%, $P < 0.001$) Mental health: suicidal thoughts (lifetime) = 41.2% (males 34.7% vs. females 49.3%, $P < 0.01$); suicidal attempts (lifetime) = 21.1% (males 12.1% vs. females 32.2%, $P < 0.001$); SCL-56 global severity score = 101.8 (males 95.5 vs. females 109.7, $P < 0.001$); Beck Depression Inventory = 15.2 (males 13 vs. females 18.1, $P < 0.001$)
Coviello, 2011 [17]	9 month follow-up 230 discharged from a MTTP in need of Tx: – 102 re-engaged – 128 not re-engaged	102 in MMT (Tx) 128 not re-engaged (NoTx): – 6 week outreach case management for re-engaging in Tx – passive referral for Tx	i.v. drug use (%): significantly lower in the Tx group (29 vs. 57, $P < 0.001$) Psychiatric treatment (average number of outpatients treatments): significantly higher in the Tx group (0.4 vs. 0.2, $P = 0.001$)
Jimenez-Treviño, 2011 [47]	25 year follow-up 214 heroin-addicts who were enrolled in MMT in 1980–84		Survivors sample (53 subjects): HIV diagnosis = 47.2% (males 46.5%, females 58.3%); hepatitis B or C = 81.1% (males 90%, females 78.6%); severity of the addiction (CGI score) = 3.76 (current MMT 2.92 vs. no MMT 4.5, $P = 0.015$; no gender differences)
Comiskey, 2010 [10]	1 year follow-up 215	3 MMTP settings: – 48 community-based clinics (CS) – 113 health board clinics (HB) – 54 general practitioners surgeries (GP)	Physical health symptoms – % of participants reporting over the preceding 90 days: no significant differences except for a significant increase in stomach pains in the HB setting (from 24% at baseline to 40% at follow-up, $P < 0.05$) and numbness/tingling in arms/legs in CS (from 14% to 33%, $P < 0.05$) Mental health symptoms – % of participants reporting over the preceding 90 days: no significant differences
Astals, 2009 [12]	18 month follow-up 189	Low-threshold MMTP	New co-occurring mental disorders: lower cumulative incidence in patients retained in the MMTP compared to those not retained (11.43% vs. 28.6%)

Table 1

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First author, year (reference)	Design, <i>n</i>	Intervention	Results
Corsi, 2009 [6]	6 month follow-up 160	MMT plus one of the following: (i) risk reduction, (ii) motivational interviewing, (iii) strengths-based case management	Needle risk behaviours: significant reduction in: (i) used dirty needles (from 36% at baseline to 20.3% at follow-up, $P < 0.001$); and (ii) shared paraphernalia (from 61.3% to 40%, $P < 0.001$) Sexual risk behaviours: significant reduction in: (i) sex with i.v. drug use (from 45.6% to 35.4%, $P = 0.005$); and (ii) sex for drugs or money (from 19.4% to 5.6%, $P < 0.001$)
Gossop, 2003 [14]	1 year follow-up 732	National Treatment Outcome Research Study (NTORS) 8 inpatient drug dependence units 15 residential rehabilitation units 16 methadone maintenance clinics 15 methadone reduction programmes	i.v. drug use (%): significantly reduction at follow-up for both the total sample (from 63% at baseline to 41% at follow-up, $P < 0.001$) and the subsample that were using drugs both at intake and at follow-up (from 64% to 53%, $P < 0.001$). For the outpatient MMTPs results were identical (from 64% to 53%, $P < 0.001$) Shared use of injection paraphernalia: significant reduction for both the total sample (from 25% to 8%, $P < 0.001$) and the subsample that were injecting drugs both at intake and at follow-up (from 25% to 14%; $P < 0.001$). For the outpatient MMTPs results were similar (from 21% to 11%, $P < 0.01$) Physical health: the greatest reduction was found in the abstinent group (from 17.8 at baseline to 6 at follow-up) and the lowest in the sharing injecting equipment (from 16.2 to 15.7) ($P < 0.001$) Mental health – anxiety: the greatest reduction was found in the abstinent group (from 2.1 to 1) and the lowest in the shared injection paraphernalia group (from 1.6 to 1.6) ($P < 0.001$) Mental health – depression: the greatest reduction was found in the abstinent group (from 2.3 to 0.9) and the lowest in the shared injection paraphernalia group (from 2 to 1.9) ($P < 0.001$)
Gossop, 2003 [18]	2 year follow-up 240	MMT settings: general practitioners (GP) or drug clinics (DC)	i.v. drug use during the previous 3 months (%): significant reductions from intake to follow-up (GP = 58% to 32%, $P < 0.001$; DC = 64% to 42%, $P < 0.001$) Sharing needles and syringes: significant reductions (GP = 9% to 4%; DC = 14% to 7%, $P < 0.05$) Physical health problems: significant reductions in both groups Psychological health problems: significant reductions in both groups ASI psychiatric composite: significant decrease at follow-up ($P = 0.003$)
Cacciola, 2001 [19]	7 month follow-up 310 opioid-dependent patients	MMT plus individual counseling	i.v. drug use during the previous year (%): significant decrease (from 92.9% at baseline to 18.6% at follow-up, $P < 0.001$) Shared use of injection paraphernalia during the previous year (%): significant decrease (from 82.1% to 7.1%, $P < 0.001$) Hepatitis B: from 78% to 90% (non significant) HIV: from 28.6% to 35.7% (non significant)
Fernandez-Miranda, 2001 [16]	6 year follow-up 132 opioid-dependents who were enrolled in MMT in 1991–92	Medium-threshold MMT	
Criminal activity			
Coviello, 2011 [17]	9 month follow-up 230 discharged from a MTTP in need of Tx: – 102 re-engaged – 128 not re-engaged	102 in MMT (Tx) 128 not re-engaged (NoTx): – 6-week outreach case management for re-engaging in Tx – passive referral for Tx	Incarceration (% since baseline): significantly lower in the Tx group (1 vs. 9, $P = 0.019$)
Deck, 2009 [20]	10 year follow-up 26 933	MMT	The probability of arrest was much lower during months in MMT compared with months untreated Long term retention was associated with greater reduction in arrests
Corsi, 2009 [6]	6 month follow-up 160	MMT plus 1 of the following: (i) risk reduction, (ii) motivational interviewing, (iii) strengths-based case management	Illegal income: significant reduction (from 41.5% at baseline to 23% at follow-up, $P < 0.001$)
Gossop, 2003 [18]	2 year follow-up 240	MMT settings: general practitioners (GP) or drug clinics (DC)	Frequency of crime: significant reductions in both groups
Cacciola, 2001 [19]	7 month follow-up 310 opioid-dependent patients	MMT plus individual counseling	ASI legal composite: significant decrease at follow-up ($P < 0.001$) Crime days: significant decrease at follow-up ($P < 0.001$)

Table 1

Continued

First author, year (reference)	Design, <i>n</i>	Intervention	Results
Functioning			
Litchfield, 2010 [21]	1 year follow-up 34 female sex-workers	MMT (usually) plus the following as required: (i) sexual health interventions and advice, (ii) specialised key working intervention, (iii) psychosocial interventions	Involvement in sex work (self-reported): reduction (from 100% at baseline to 33% at follow-up)
Corsi, 2009 [6]	6 month follow-up 160	MMT plus 1 of the following: (i) risk reduction, (ii) motivational interviewing, (iii) strengths-based case management	Productivity: significant increase in employment rate (from 32.5% at baseline to 47.5% at follow-up, $P < 0.001$)
Cacciola, 2001 [19]	7 month follow-up 310 opioid-dependent patients	MMT plus individual counseling	ASI family/social composite: significant decrease at follow-up ($P = 0.012$) Days paid for work: significant increase at follow-up ($P = 0.016$)
Quality of life			
Grella, 2012 [8]	30 year follow-up 343 subjects who were enrolled in MMT at some point in 1976–78		Men: ages 45–54 years = significantly lower HRQoL than population norm in the following SF-36 subscales: role functioning physical, bodily pain, general health, energy and fatigue and social functioning. Those who used drugs in the past year showed significantly lower HRQoL in physical functioning; ages 55–64 years = significantly lower HRQoL than population norm in all SF-36 subscales but role functioning emotional. Those who used drugs in the past year showed significantly lower HRQoL in bodily pain; ages 65 + years = no differences with population norms Females: ages 45–54 years = significantly lower HRQoL than population norm in all SF-36 scales. Those who used drugs in the past year showed significantly lower HRQoL in emotional well-being; ages 55–64 years = significantly lower HRQoL than population norm in all SF-36 scales. Those who used drugs in the past year showed significantly lower HRQoL in role functioning emotional
Litchfield, 2010 [21]	1 year follow-up 34 female sex-workers	MMT (usually) plus the following as required: (i) sexual health interventions and advice, (ii) specialized key working intervention, (iii) psychosocial interventions	Christo Inventory score: significant reduction (from 12.5 at baseline to 8.97 at follow-up, $P < 0.001$), meaning a significant improvement in well-being

ASI, Addiction Severity Index; CGI, Clinical Global Impression; HIV, human immunodeficiency virus; HRQoL, Health Related Quality of Life; MMT, maintenance methadone treatment; MMTP, maintenance methadone treatment programme; RR, relative risk; SF-36, the MOS 36-item Short-Form Health Survey; THC, tetrahydrocannabinol; Tx, treatment.

drug-seeking behaviours in those patients with a long history of treatment attempts and failures. It has been claimed to increase retention in treatment, limit the use of street drugs, reduce illegal activities and possibly improve health and reduce mortality. In Europe diarmorphine is approved for the treatment of treatment-refractory heroin addiction patients in Denmark, Germany, the Netherlands, the United Kingdom and Switzerland, and in Canada diacetylmorphine has approval for research trials only [26].

The majority of studies on HAT are randomized controlled trials comparing injected HAT vs. optimized oral/injected MMT in patients considered resistant to methadone treatment (see Table 3). Although results are discrepant, a tendency exists toward greater retention rates for the HAT group, ranging from 90.4% at 1 year [27] to 55.7% at 4 years of follow-up [28].

Results for illicit drug use were similar, i.e. patients receiving HAT showed greater significant reductions in the number of days of illicit heroin use [28–33] and greater improvements in drug use scores [27] compared with patients on MMT. Furthermore, patients who received HAT at any point showed a greater significant decrease in the use of cannabis compared with patients who never received HAT [27].

With respect to HIV risk behaviours, a study conducted in Spain demonstrated greater reductions in these behaviours among patients on HAT [29, 30]. In addition, HAT was associated with greater improvements in both physical and mental health [27, 29–31], illegal activity [30], employment satisfaction [27], and quality of life [27, 29, 30]. However, no differences were found in social and family functioning between MMT and HAT [30].

Table 2

Long term outcomes of buprenorphine and buprenorphine/naloxone maintenance treatment for opioid dependence

First author, year (reference)	Design, n	Intervention	Results
Retention in treatment, drug use and overdose			
Curcio, 2011 [22]	1 year follow-up 3812 drug addicts	MMT: 3105 patients Bup/Nx MT: 707	1 year retention rate: MMT = 92.5%; Bup/Nx MT = 89.4% ($P = 0.369$) Substance use: opioid and cocaine negative urine tests: MMT = 30%; Bup/Nx MT = 53% ($P < 0.001$)
Parran, 2010 [24]	18 month follow-up 176 induced patients 110 followed-up	Bup/Nx MTP: – Primary phase: 23–48 h inpatient induction plus (i) 5 weeks of intensive outpatient counseling, plus (ii) 12 weeks of weekly once aftercare sessions – Outpatient phase: monthly visits with 12-step meeting attendance	18 month retention rate = 77% Substance use: continued Bup/Nx patients were less likely to report using heroin ($P = 0.004$) and any drug ($P = 0.012$)
Soeffing, 2009 [23]	12 month follow-up 255 patients, primary care setting	Sublingual BMT plus brief supportive interventions	1 year retention rate = 56.9%; Significantly greater retention rate for patients using cocaine ($P = 0.011$), alcohol ($P = 0.041$), and assigned to attending or resident physicians ($P = 0.012$)
Health status and risk behaviours			
Altice, 2011 [25]	12 month follow-up 295 HIV-infected opioid-dependent patients	Bup/Nx MT	Improved prescription of ART, HIV suppression and CD4 lymphocyte changes were not significantly associated with longer retention on Bup/Nx MT For those who were not on ART at baseline retention on Bup/Nx MT for ≥ 12 month was significantly associated with greater likelihood of initiating ART and with achieving viral suppression
Functioning			
Curcio, 2011 [22]	1 year follow-up 3812 drug addicts	MMT: 3105 patients Bup/Nx MT: 707	Improvement in social life status (married/cohabiting): MMT = 39%; Bup/Nx MT = 63% ($P < 0.001$), and in educational level (at least high school certificate): MMT = 32%; Bup/Nx MT = 43% ($P < 0.001$)

ART, antiretroviral therapy; BMT, buprenorphine maintenance treatment; Bup/Nx MT, buprenorphine/naloxone maintenance treatment; Bup/Nx MTP, buprenorphine/naloxone maintenance treatment programme; HIV, human immunodeficiency virus; MMT, methadone maintenance treatment.

Levo-alpha-acetyl-methadol (LAAM) Levo-alpha-acetyl-methadol (LAAM) is a synthetic opioid agonist effective in the treatment of opioid addiction. It was approved by the Food and Drug Administration in 1993. Its main advantage over methadone is its longer active half-life, which gives patients a longer interval between doses, thus suggesting a longer retention in treatment than with methadone. However, a meta-analysis of randomized controlled trials comparing methadone and LAAM showed a small treatment difference favouring methadone [34].

In 2001, due to its cardiovascular adverse reactions (significant QT_c interval prolongation and severe arrhythmia), the European Medicines Agency (EMA) suspended the marketing authorization of Orlaam and advised physicians to switch their patients from Orlaam to other options, e.g. methadone [35].

Discussion

In the last decade the maintenance treatment for opioid dependence has been evolving and progressing due to

two different factors: on one hand, the development of novel therapeutic approaches and on the other hand, changes in regulatory issues [36]. In this paper we review the available evidence on the current pharmacological treatment options. Even though there are inconsistencies in the studies reviewed, mainly related to the design, the patients included, outcome measures used and interventions performed, their results allow us to characterize the long term outcomes and the clinical profile of each of the three options reviewed, i.e. methadone, buprenorphine and buprenorphine/naloxone, and heroin-assisted treatment.

With regard to methadone, research has shown that it is useful in increasing retention in treatment, physical and mental health levels, functioning and quality of life, and in decreasing the use of illicit drugs and HIV risk behaviours. In fact, in 2009, the World Health Organization Guidelines recommended methadone and buprenorphine as first line agents for agonist maintenance treatment [37].

Methadone has demonstrated its effectiveness in different practice settings (physician offices, specialized clinics) and with different MMT programmes (low or

Table 3

Long term outcomes of heroin-assisted treatment for opioid dependence

First author, year, country (reference)	Design, n	Intervention	Results
Retention in treatment, drug use, overdose and mortality			
Rehm, 2005, Switzerland [48]	7 year follow-up, observational cohort study Heroin-assisted patients between 1994 and 2000		Standard Mortality Rate 1994–2000 = 9.7 (CI = 7.3–12.8)
March, 2006, Spain [30]	9 month follow-up, randomized controlled trial 62 opioid-injecting patients not responding to at least two trials of methadone with severe concomitant problems	Injectable HAT (n = 31) Oral MMT (n = 31)	9 month retention rate: no significant differences between groups Illegal heroin use (days per month): significant reduction in both groups ($P = 0.001$, $P = 0.021$). Significantly greater reduction in the HAT group (15.3 vs. 6.5, $P = 0.20$)
Oviedo-Joekes, 2010, Spain [29]	2 year follow-up, observational cohort study 54 opioid-injecting patients not responding to methadone with severe concomitant problems	Currently on HAT (n = 24) Discontinued HAT (n = 18) Never on HAT (n = 12)	Illicit heroin use in the prior month: significant decrease from baseline in the three groups ($P < 0.05$), and those currently on HAT used illicit heroin significantly fewer days than the other two groups (2.4 vs. 6.6 vs. 13.9, $P < 0.001$) Cannabis use in the prior month: those who received HAT at any point used cannabis significantly fewer days than those who never received HAT (10.3 vs. 9.6 vs. 18.8, $P = 0.042$)
Haasen, 2007, Germany [31] GToHAT	1 year follow-up, randomized controlled trial 1015 heroin-dependent patients (528 not in treatment and 487 with methadone treatment failure)	Injectable HAT (n = 515) plus (i) education or (ii) case management Oral MMT (n = 500) plus (i) education or (ii) case management	1 year retention rate: higher in the heroin group (67.2% vs. 40%) Illegal drug use: significantly greater reduction in the heroin group (69.1% vs. 55.2%, $P < 0.001$)
Eiroa-Orosa, 2010, Germany [49] GToHAT	1 year follow-up, randomized controlled trial 1015 heroin-dependent patients (528 not in treatment and 487 with methadone treatment failure)	Injectable HAT (n = 515) plus (i) education or (ii) case management Oral MMT (n = 500) plus (i) education or (ii) case management	Benzodiazepine use (positive urine tests): significantly greater reduction in the heroin group ($P < 0.0001$) In the heroin group, significantly higher retention rate in those who did not use benzodiazepines at baseline (74.1% vs. 64.5%, $P = 0.38$) Illegal drug use: no significant differences according to use/non use of benzodiazepines at baseline in both heroin and methadone treatment groups
Oviedo-Joekes, 2008, Canada [27] NAOMI	1 year follow-up, randomized controlled trial 226 long term treatment-refractory opioid-dependent patients	Injected DAM (n = 115) Oral MMT (n = 111)	1 year retention rate: significantly higher in DAM in both females (83.3% vs. 47.8%, $P < 0.01$) and males (90.4% vs. 58.5%, $P < 0.01$) Drug use: Females in the DAM group improved significantly more than those in the MMT (EuropASI: -0.064 , $P < 0.05$) Males in the DAM group improved significantly more than those in the MMT (EuropASI: -0.072 , $P < 0.05$)
Strang, 2010, United Kingdom [33] RIOTT	26 week follow-up randomized controlled trial 127 patients on oral substitution treatment and injecting illicit heroin on a regular basis	Optimised oral MMT (n = 42) Injected MT (n = 42) Injected HAT (n = 43)	26 week retention rate: no statically significant differences (Optimized oral MMT = 69%, injected MT = 81%, injected HAT = 88%) Illegal heroin use (responder: $\geq 50\%$ negative urine tests): significantly greater responder rates in the injected HAT than in the optimised oral MMT group (72% vs. 27%, $P < 0.0001$, OR = 7.42, NNT = 2.17). No differences between injected and oral methadone
Blanken, 2005, the Netherlands [50]	1 year follow-up randomized controlled trial 430 heroin addicts	MMT MT plus injected HAT + MT plus inhalable HAT	Response to treatment (multi-domain index: illicit substance use and physical, mental and social health): MT + HAT (injected or inhaled) had a significantly better response than MMT (51.8% vs. 28.7%)
Blanken, 2010, the Netherlands [28]	4 year follow-up, observational cohort study 149 heroin-dependent patients with positive response to short-term HAT	Long-term HAT	4 year retention rate: 55.7% Response to treatment (multi-domain index: illicit substance use and physical, mental and social health): those who continued 4 years in treatment had a significantly better response than those who discontinued treatment (90.4% vs. 21.2%)
Blanken, 2012, the Netherlands [32]	1 year follow-up, randomized controlled trial 73 chronic treatment-refractory heroin-dependent patients	Co-prescribed injectable or inhalable HAT Continued oral MMT	Heroin use (days of illicit heroin use in the previous month): greater decline after baseline in the HAT group Heroin craving: significant decrease at follow-up in the HAT group ($P < 0.001$) compared with MMT

Table 3

Continued

First author, year, country (reference)	Design, n	Intervention	Results
Health status and risk behaviours			
March, 2006, Spain [30]	9 month follow-up, randomized controlled trial 62 opioid-injecting patients not responding to at least two trials of methadone with severe concomitant problems	Injectable HAT (n = 31) Oral MMT (n = 31)	HIV risk behaviours (OTI scores): significant decrease in general ($P = 0.001$) and related to drug use ($P = 0.001$, $P = 0.000$) HIV risk behaviours in both groups. Patients in the injectable HAT group showed a greater significant decrease in both behaviours ($P = 0.012$, $P = 0.004$) General health (OTI score): significant improvement in the injectable HAT group ($P = 0.001$) Mental health (ASI and SCL-90 scores): significant improvement in both groups ($P < 0.01$). No differences between groups
Oviedo-Joekes, 2010, Spain [29]	2 year follow-up, observational cohort study 54 opioid-injecting patients not responding to methadone with severe concomitant problems	Currently on HAT (n = 24) Discontinued HAT (n = 18) Never on HAT (n = 12)	HIV risk behaviours (OTI score): Those who received HAT at some point decreased their HIV risk significantly more than those who never received HAT ($P = 0.045$) Those currently on HAT significantly decreased their HIV risk behaviours (10.9 vs. 2.8, $P < 0.05$) Mental health (ASI psychiatric composite score): Those currently on HAT significantly improved their mental health (ASI baseline = 0.5 vs. 6 month = 0.3, $P < 0.05$). Furthermore, their mental health was significantly better than the other two groups ($P = 0.030$)
Haasen, 2007, Germany [31] GToHAT	1 year follow-up, randomized controlled trial 1015 heroin-dependent patients (528 not in treatment and 487 with methadone treatment failure)	Injectable HAT (n = 515) plus (i) education or (ii) case management Oral MMT (n = 500) plus (i) education or (ii) case management	Health status: a significantly greater proportion of patients showed an improvement in health status (physical and mental) in the heroin group (80% vs. 74%, $P = 0.023$)
Oviedo-Joekes, 2008, Canada [27] NAOMI	1 year follow-up, randomized controlled trial 226 long-term treatment-refractory opioid-dependent patients	Injected DAM (n = 115) Oral MMT (n = 111)	Physical health: Males in the DAM group improved significantly more than those in the MMT (EuropASI medical status: -0.135 , $P < 0.05$) Psychological health: Females in the DAM group improved significantly more than those in the MMT (EuropASI psychiatric status: -0.081 , $P < 0.05$ and MAP psychological: -2.454 , $P < 0.05$) Males in the DAM group improved significantly more than those in the MMT (EuropASI psychiatric status: -0.047 , $P < 0.05$)
Criminal activity			
March, 2006, Spain [30]	9 month follow-up, randomized controlled trial 62 opioid-injecting patients not responding to at least two trials of methadone with severe concomitant problems	Injectable HAT (n = 31) Oral MMT (n = 31)	Illegal activities (number of days per month): significant improvement in both groups ($P < 0.01$). No differences between groups
Functioning			
March, 2006, Spain [30]	9 month follow-up, randomized controlled trial 62 opioid-injecting patients not responding to at least two trials of methadone with severe concomitant problems	Injectable HAT (n = 31) Oral MMT (n = 31)	Family functioning (ASI score): significant improvement in both groups ($P < 0.01$). No differences between groups Social functioning (OTI score): significant improvement in both groups ($P < 0.01$). No differences between groups
Oviedo-Joekes, 2008, Canada [27] NAOMI	1 year follow-up, randomized controlled trial 226 long term treatment-refractory opioid-dependent patients	Injected DAM (n = 115) Oral MMT (n = 111)	Employment satisfaction: Males in the DAM group improved significantly more than those in the MMT (EuropASI employment: -0.092 , $P < 0.05$)
Quality of life			
March, 2006, Spain [30]	9 month follow-up, randomized controlled trial 62 opioid-injecting patients not responding to at least two trials of methadone with severe concomitant problems	Injectable HAT (n = 31) Oral MMT (n = 31)	Perceived health (SF-12 physical and mental health scores): Physical health: significant improvement in the injected HAT group ($P = 0.001$) Mental health: significant improvement in the oral MMT group ($P = 0.023$)

Table 3

Continued

First author, year, country (reference)	Design, n	Intervention	Results
Oviedo-Joekes, 2010, Spain [29]	2 year follow-up, observational cohort study 54 opioid-injecting patients not responding to methadone with severe concomitant problems	Currently on HAT (n = 24) Discontinued HAT (n = 18) Never on HAT (n = 12)	Perceived mental health (SF-12 mental health score): Those currently on HAT significantly improved their perceived mental health (SF-12 baseline = 30.5 vs. 6 month = 40.1, $P < 0.05$). Furthermore, self-perceived mental health was significantly better than the other two groups (SF-12 $P = 0.004$)
Oviedo-Joekes, 2008, Canada [27] NAOMI	1 year follow-up, randomized controlled trial 226 long-term treatment-refractory opioid-dependent patients	Injected DAM (n = 115) Oral MMT (n = 111)	Quality of life: Males in the DAM group improved significantly less than those in the MMT group (EQ5D: 0.065, $P < 0.05$ and SF-6D: 0.049, $P < 0.05$)

ASI, Addiction Severity Index; DAM, diacetylmorphine; EQ5D, EuroQol 5-Dimensions; EuropASI, European version of the Addiction Severity Index; GToHAT, German Trial on Heroin-Assisted Treatment; HAT, heroin assisted treatment; HIV, human immunodeficiency virus; MAP, Maudsley Addiction Profile; MMT, methadone maintenance treatment; MT, methadone treatment; NAOMI, North American Opiate Medication Initiative; NNT, number needed to treat; OR = odds ratio; OTI = Opiate Treatment Index; RIOTT, Randomized Injecting Opioid Treatment Trial; SCL-90, Symptom Check-List-90; SF-12, the MOS 12-item Short-Form Health Survey; SF-6D, the MOS 6D Short-Form Health Survey.

medium threshold, optimized programmes), although studies have shown that high doses are needed to eliminate heroin use [38]. Its potential serious adverse events include slight prolongation of the QT_c interval and respiratory depression, and although the mortality rate increases during the first 2 weeks of treatment, there is a progressive reduction afterwards [38]. Due to its overdose toxicity, the initial dose of methadone should be under 40 mg day⁻¹ with slow increases (up to 20 mg week⁻¹) over long periods of time (up to 6 weeks) until reaching the maintenance dose that eliminates heroin use (60–120 mg day⁻¹) [37, 39].

There is copious evidence of the efficacy and safety of buprenorphine and buprenorphine/naloxone [40]. Comparative studies with methadone have generally reported a slight advantage for methadone [41], although some recent studies have found the opposite [22]. In any event, its ease of administration and its approval as a community-based treatment have made a change in the treatment of opioid dependence, increasing the number of heroin addicts receiving treatment [42]. Indeed, it was the first opioid agonist approved for opioid dependence treatment in primary care offices in the U.S [43]. On the other hand, buprenorphine seems to be superior to methadone in its better tolerability profile, lower risk of overdose and recreational use, and ease of use [24], thus making it a good option for use in outpatient primary care offices.

Due to its relatively widespread availability, there are risks of accidental overdose, misuse and abuse. Of particular concern is the risk of accidental overdose in children since it can cause fatal respiratory depression. For this reason, in view of the significantly higher rates of accidental paediatric exposure to Suboxone tablets compared with Suboxone film, Reckitt Benckiser Pharmaceuticals Inc. voluntarily withdrew Suboxone tablets from the market in the United States. Furthermore they issued a Citizen

Petition requesting the Food and Drug Administration to 'require all manufacturers of buprenorphine-containing products for the treatment of opioid dependence to implement national public health safeguards involving paediatric exposure educational campaigns and child resistant, unit-dosed packaging to reduce the risk of paediatric exposure' [44].

Heroin research has demonstrated that it is a feasible treatment for patients with heroin abuse and long term heroine dependence who are refractory to treatment. Refractory to treatment is generally described as lack of response to at least two trials of methadone and the presence of concomitant severe physical, mental, social and/or functional problems. In this subgroup of patients, although the evidence is inconclusive, several studies have found heroin to be superior to methadone in obtaining positive long term outcomes on several indicators such as mortality rate, retention rate, use of illegal heroin and/or other substances of abuse, HIV risk behaviours, and physical and mental health. However, it is necessary to bear in mind that these results were obtained in a highly select subgroup of patients treated under specific clinical conditions in certain countries with a well-developed and comprehensive system for the treatment of opioid dependence. Furthermore, concerns about its safety, both for patients (respiratory depression, seizures) and society (diversion and trivialization), have been claimed, although the results of the studies do not support them [45]. However, Haasen *et al.* [31] found that serious adverse events occurred 2.5 times more often in the heroin group compared with the methadone group.

Concerns also exist with respect to the philosophy underlying this medical treatment option. If the basis for maintenance treatments is that patients will regain the control over their heroin use by prescribing them a

substitute such as methadone or buprenorphine [3], then if physicians prescribe heroin to heroin addicts, such control will never be achieved. Furthermore, McKeganey [46] questioned why cocaine addicts cannot have cocaine provided in the same way as heroin is provided to heroin addicts.

Another pharmacotherapy for opioid dependence that has the potential to be used as a long term treatment is depot naltrexone. Given its opioid antagonist effect, it may be an excellent candidate for long term relapse prevention treatment. It was not reviewed here because it is approved only in a few countries and there are no data about its use as a long term treatment. Hopefully data will be available in the near future showing the efficacy and safety of this medication.

The available evidence shows that the three pharmacological maintenance treatment options reviewed here are effective and each has its specific profile and target population. However, implementation of the novel approaches into clinical practice is still rather limited [42], preventing heroin-dependent patients from benefitting from them.

We think that the field of opioid dependence treatment is poised to undergo a process of reinforcement and transformation that will enable clinicians to match the right maintenance treatment option to the needs and profile of each individual patient. For this reason, further efforts from researchers, clinicians and authorities should be made to turn new pharmacological options into clinical reality and to overcome the structural and functional obstacles that maintenance programmes face in combatting opioid dependence.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

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